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14. ABSTRACT

Breast Cancer remains a leading cause of death for women in the US despite the popularity of mammography as a preventive tool. At diagnosis, many breast cancers are at an advanced stage of disease, even for women undergoing annual screening, resulting in costly and painful follow-up procedures. It has been shown that molecular markers can increase our ability to diagnose early stages tumors. This has been demonstrated by current clinical practices using the CA-125 marker and PSA for the detection of ovarian and prostate cancer, respectively. The purpose of this study is to search for breast cancer biomarkers and evaluate their effectiveness in detecting early stage carcinoma. By combining molecular diagnosis with current imaging analysis of breast tissue, we may further reduce the number of deaths as well as the number of women undergoing surgery due to breast cancer. To date, we have created the infrastructure necessary for our interdisciplinary team of investigators to obtain study samples from a well-characterized population, analyze candidate biomarkers, and efficiently communicate research findings. We are also exploring more efficient and sensitive biotechnology that may better assist our study investigators.

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Introduction

Although mammography significantly reduces its toll, breast cancer remains a leading cause of cancer mortality in the U.S. Many breast cancers are advanced at the time of diagnosis, even among women participating in screening. The discovery of molecular markers associated with breast cancer potentially increases our ability to diagnose early stage tumors. We are proposing that molecular diagnosis be combined with imaging to enhance our ability to identify breast cancer when it is most treatable, i.e. still localized to the breast. This study will test the hypothesis that use of a breast cancer serum biomarker panel can improve the performance of mammography in early detection of breast cancer. The primary aims of the study are: 1) to validate and refine the ability of candidate biomarkers measurable in blood products to predict disease status; 2) to evaluate panels of serum markers for use as an adjunct to mammography, to detect all breast cancer at a highly curable stage; and 3) to identify the molecular signatures of benign, pre-invasive and invasive breast tissue and explore their associations with serum markers in the panel.

We are focusing on markers that can be measured in serum, as they are generally inexpensive and not subjective in their interpretation. To avoid over-diagnosis, we will perform molecular profiling to identify aggressive subsets of breast cancer that are most likely to be missed by mammography and in need of early detection. Our current list of candidate markers includes circulating antibodies to oncogenic proteins known to be associated with aggressive disease such as Her2/neu, and IGFBP-2; and circulating tumor markers including growth factors associated with angiogenesis such as VEGF, DNA methylation markers, lipid markers, CD24, Psoriasin (S100 A7), Mammaglobin, and a panel of 10+ cytokines. At the end of this Center of Excellence study, the expected result is a panel of markers and decision rules for its use clinically to improve the performance of mammography.

Body

As previously reported, we began clinical recruitment activities at FHCRC in May, 2004. Since that time we have been actively recruiting women into the mammography and surgical cohorts (see tasks 1 and 3 respectively). The mammography cohort is comprised of women having screening mammograms and women having breast biopsies. For women receiving annual mammograms, we are using their mammography data (assessment codes, follow up recommendations, and breast density) in coordination with family history collected on our baseline questionnaire and the GAIL model to determine risk of breast cancer (high, elevated or average risk). The surgical cohort consists of women scheduled to undergo breast surgery, for malignant or nonmalignant conditions. In July, 2005 we also received approval to begin surgical recruitment at Cedars-Sinai Medical Center in Los Angeles. Recruitment efforts at Cedars-Sinai are led by Drs. Beth and Scott Karlan. The clinical protocols for each site have been standardized as much as possible. Each site uses common data collection instruments and a shared, web-enabled data entry system called the Seattle Informatics Management System (SIM) to collect questionnaire data as well as information on donated specimens.

Our patient advocate coordinator, Shannon Marsh, continues to play an important role in our COE. Over the last year, Ms. Marsh has worked closely with Dr. Urban and COE staff members to develop and refine study materials. Ms. Marsh has also been working on community outreach materials including quarterly *Women's Cancer Prevention and Detection* newsletters, which are sent to all women in our Women's Cancer Prevention and Detection Network, as well as all women participating in our COE (see Appendix A). Ms. Marsh helps to coordinate patient advocate involvement at all COE investigator

meetings with at least one to two advocates participating to ensure that the patient perspective is always represented and heard. In the long term, we envision that Ms. Marsh and other COE patient advocates will work with COE investigators to help determine how best to use markers clinically.

In 2005, we began organizing quarterly COE investigator meetings that included consumer advocate participation, as mentioned above, as well as staff involvement. Each meeting focused on a topic relevant to the overall study: clinical impact and applications of biomarkers, biomarkers and laboratory developments, and informatics. The final meeting of the year is the Annual COE Workshop held in Seattle on the Hutchinson Center campus. All meetings include presentations by study investigators, collaborators and outside experts on work relevant to the aims of the COE with additional time allowed for discussion.

The 2005 COE Workshop was held last October (see Appendix B for meeting agenda). We are currently planning the 2006 COE investigator workshop, which will be held on November 3rd. Current confirmed speakers include Dr. Bruce Porter, director of First Hill Medical Imaging in Seattle who will speak about the principals of and indications for breast MRI, Dr. Hailing Lu from Dr. Disis's lab, who will speak about a tumor antigen repertoire in mice that predicts human tumor antigen, and Dr. Scott Karlan, a co-investigator on the COE and breast surgeon at Cedars-Sinai Medical Center who will present data on the usefulness of expression array technology to assist in the selection of adjuvant therapy.

In July, 2006 Dr. Urban attended the BCRP Centers of Excellence meeting in Arlington, VA along with Dr. David Beatty, a fellow investigator and breast surgeon at Swedish Medical Center, Dr. Nathalie Scholler, and Ms. Kate Watabayashi, the study coordinator. At the meeting, Dr. Urban invited other COE investigators to discuss possible collaborations to validate promising breast markers. Dr. Sukumar and Dr. Tlsty are some of the potential collaborators who responded to this request. During the coming year we plan to complete development of a Breast Mini-Triage Set (formerly called Assay Refinement Triage Set - ARTS) that will be used to evaluate these and other candidate markers for inclusion in a biomarker panel (see Task 10 for more details).

Clinical use of a marker panel is a complex area of study that requires integration of all of the information from marker analyses and molecular profiling as well as economic and health systems considerations. It is critical to understand what we want our biomarker panel to detect. The latter considerations are being studied through a micro simulation model that was developed through a previously funded DoD grant (DAMD17-94-J-4237). We are currently using the model to investigate the impact of DCIS detection and treatment on breast cancer mortality and associated over diagnosis. Specifically, the model is being used to generate disease histories, including disease onset, progression to diagnosis, and mortality, for a cohort of women in the United States. Mammography screening schedules are superimposed on these disease histories, allowing investigation of the efficacy of early detection of breast cancer, including the in situ stage. Cancer incidence data are combined with data from autopsy studies to estimate the prevalence of breast cancer, including DCIS, in the population. Model parameters are selected to replicate diagnosis patterns reported in published studies.

Using available data for breast cancer growth rates, mammography performance, and stage-specific survival, our analyses suggest that mammography use, including detection of DCIS at current rates, yields a 25% reduction in breast cancer mortality. We estimate that detection of DCIS accounts for over 20% of this reduction (5.6%), that 64% of screen-detected DCIS would remain latent until death due to other causes (over-diagnosis), and that mammography detects only one fifth of the prevalent DCIS. These

results are reported in a manuscript titled *Quantifying Risks of Breast Cancer Mortality and Overdiagnosis due to Mammography-diagnosed DCIS* that will be submitted during the next funding period.

Below we outline each task included in our Statement of Work and detail efforts toward completion of each task. In September 2006, we received a cost-extension extending this study for 12 additional months; therefore, this report represents our progress report for our 4th year of funding (months 37-48).

TASK 1: Recruit women undergoing mammography to donate serial blood samples (Mammography Cohort)

Task 1a: Obtain Consent to Contact and Screening Questionnaire from women undergoing mammography at participating facilities (months 22-60). This task is currently underway. To date, we have collected 1,939 consent to contact forms and have sent each participant a short, one page screening questionnaire to collect preliminary risk information. 66% of the screening questionnaires have been returned. Information from these forms is entered into the Seattle Informatics Management system (SIM), and is used to invite eligible women into the COE study.

In 2006, we began placing "join the network" brochures (consent to contact forms) on the Swedish Medical Center's Mobile Mammography Coach. Part of the coach's mission is to provide health services to minority and underserved populations in the community and we have partnered with them in an effort in increase the diversity of women who provide their consent to be contacted about research studies.

Task 1b: Obtain mammography data from participating facilities (month 22 and quarterly thereafter). This task is currently underway. We obtained our first electronic data download in December of 2004 from Swedish Medical Center's Mammography Reporting System (MRS). This system is used by all Swedish Medical Center radiology facilities. The first download contained 288,000 electronic mammography exam records. As reported last year, we have created a Mammography Data Collection Form and a data entry screen on SIM that is used to capture specific mammography data on our study participants. During the last year we have run a linking algorithm to match study participants to their mammography results from MRS. Using this data we have been able to incorporate mammography information such as assessment code, density and follow-up recommendations into our risk algorithm. If a woman does not receive her annual mammograms from a facility that uses MRS, then we have procedures in place to request hard copies of mammography reports directly from her radiology facility. Study staff are trained to abstract data from the reports and enter a woman's information directly into SIM. To date approximately 81% of our participants are in the MRS system.

We have arranged to receive updated electronic mammography data every 3 months from participating facilities. Collected data is stored on a password-protected network drive, accessible only to authorized personnel who have signed a confidentiality agreement.

Task 1c: Using on-going sampling technique, stratify population by risk (month 37 and quarterly thereafter). As reported above, we have collected 1,939 Consent to Contact ("join the network") forms and have received completed screening questionnaires from about 66% of these women. If determined eligible, women are sent a COE study invitation packet. To date, we have invited 1,213 women to participate in the study as part of the mammography cohort with 599 or 49% enrolling into the study.

Information collected on our study questionnaires and mammography results are used to stratify our study population by risk; that is, allowing us to characterize a woman as high

elevated or average risk. A woman is determined to be at high risk based on family history, if she is of Ashkenazi Jewish decent, self-reports a positive test for the BRCA 1 or BRCA 2 mutation, or as prior history of receiving a breast biopsy. A woman is determined to be at elevated risk for breast cancer using the GAIL Model, breast density, mammography assessment codes, or mammography follow-up recommendations. The table below summaries the number of women enrolled into the mammography cohort and associated risk levels based on collected information.

Table 1. Mammography Cohort patients who completed a risk factor/baseline questionnaire

Risk Level	Participants	% of Enrolled
High Risk	121	20%
Elevated Risk	317	53%
Average Risk	36	6%
Risk status pending (data has not yet been abstracted)	125	21%
Total	**599**	**100%**

Task 1d: Approach selected women for blood donation (months 25-66). This task has been underway since October, 2004. Of the 599 women enrolled in the COE mammography cohort, 80% or 482 women have completed their first blood donation. Specimen Collection Specialists work directly with study participants to schedule their blood donation appointments on or around the day of their annual mammogram.

Task 1e: Send blood donation appointment letters and epidemiologic risk factor questionnaires to consenting women (months 27-72). This task has been underway since December, 2004. As mentioned above, 482 women have completed a study blood draw. All of these women have received an epidemiologic risk factor (baseline) questionnaire. Of the 482 women, 467 participants (97%) have sent back a completed questionnaire. Some participants had already completed the same baseline questionnaire for a related study (that is, baseline data is already entered into SIM) and are not asked to complete it again for the COE. Study participants also receive a shorter health status questionnaire which provides an update on medical history and asks about factors that might affect their biomarker levels at the time of the draw. We request that study participants complete the health status questionnaire during their study appointment whereas the longer baseline questionnaire is typically sent home with the woman to complete and mail back to the study office at a later date.

Women are asked to donate blood and complete study questionnaires once a year for up to four years. 197 participants in the mammography screening population have completed a second draw. This month we will begin sending third appointment reminder letters for blood donation to study participants due for their annual mammograms in October and November. At each follow-up appointment study participants are asked to complete another health status questionnaire to update information that might change (ex. Personal and family history of cancer).

Task 1f: Receive and data enter questionnaires (months 26-76). As stated above, to date, 467 participants have completed baseline questionnaires and 480 patients have completed one or more health status questionnaires at the time of their initial or subsequent blood draws. Quality control data entry is performed on all baseline questionnaires and approximately 10% of the health status questionnaires. The database manager periodically reviews quality control data entry on all questionnaires to (describe checking error rate and making sure we are qc'ing enough questionnaires)

TASK 2: Recruit women undergoing stereotactic biopsy to donate pre-biopsy and serial follow-up blood samples (Biopsy Cohort)

Task 2a: Finalize approach procedures to be used by Swedish Breast Care Center (completed). In September 2001, Dr. Urban received funds from an NCI-Avon "Progress for Patients" award that allowed us to develop and test procedures to recruit and enroll women who were undergoing stereotactic biopsy at the Swedish Breast Care Center (SBCC). For this "Avon study" women were asked to provide a one-time only pre-biopsy blood donation and complete both the baseline and health status questionnaires. To date, we have successfully enrolled 136 women at the Swedish Breast Care Center. We will use the same procedures to recruit and enroll women into the COE Biopsy cohort. Women enrolled into the COE will be asked to give a blood sample prior to their biopsy procedure *in addition* to an annual sample at the time of subsequent mammograms.

Task 2b: Research Nurse or Specimen Collection Specialist attends biopsy appointments to obtain informed consent, collect pre-biopsy blood sample, and provide epidemiologic risk factor questionnaire (months 38-72). As stated above we are well-positioned to begin our COE biopsy recruitment efforts. In December, 2005 we revised our study protocol and materials to include recruitment at multiple Swedish Medical Center facilities instead of focusing our efforts just at the SBCC. This change was made to help us meet our recruitment goals for this population. Additional changes were also made to the recruitment procedures to better accommodate patient flow at all participating facilities. Due to the slowness of human subjects review, we have yet to implement our biopsy enrollment procedures; however, we anticipate receiving final approvals from both our internal IRB and the DoD human subjects reviewer on all protocol modifications shortly and hope to begin biopsy enrollment by Dec. 2006.

TASK 3: Recruit women undergoing surgery to donate pre-surgery and follow-up blood samples, and collect tissue on selected breast cancer cases (Surgical cohort).

Task 3a: Work with surgeons' offices to integrate patient approach procedures into the patient care flow. (completed). We have worked closely with participating breast surgeons and clinic staff to design and implement patient approach procedures for recruitment that have proven to be successfully integrated with normal clinic flow. Currently, we have 6 physicians who are referring patients to our study. Our study staff are able to maintain an open dialogue with participating physicians about study progress and procedures by checking in with them and their staff on a daily basis. This creates an environment where physicians and study staff are able to work together to continuously refine and improve our approach procedures.

Collaborating physicians are also invited to participate in COE investigator meetings and the annual All-Investigator Workshop where they are given an opportunity to ask questions and raise any issues or concerns they may have about the study.

Task 3b: Pilot patient approach and specimen collection procedures (completed).

Patient approach began in July, 2004. Following our approved protocol, Swedish Medical Center surgeons help to identify patients that are likely candidates for surgical specimen collection. At the time of the pre-surgical visit, surgeons may introduce study participation to their patients. A Study Flyer is posted in clinic offices to advertise the study. The flyer instructs interested patients to discuss participation with their physician. If the patient is interested, the physician will then obtain verbal consent for study staff to contact the patient either in person or by phone. At this time, the physician may choose to distribute a study packet containing a study brochure and a cover letter. If a study staff

member is present at the clinic, the physician invites the woman to speak to a study representative directly who can help answer immediate questions or concerns. If the patient chooses, she may also be enrolled at this time (if she meets the eligibility requirements). Otherwise, study staff contact her later by phone to discuss the study in further detail and set up an enrollment appointment to conduct in-person informed consent and collect a pre-surgical blood sample.

Task 3c: Routinely approach selected women undergoing surgery for blood and tissue collection or blood only collection (Months 24-72). This task is currently underway. To date, we have enrolled 269 participants at FHCRC into the surgical cohort. Of the total number of women who are enrolled in the study, 26% have successfully completed questionnaire data and donated blood and tissue, and another 54% have complete questionnaire data and have given at least one blood donation.

Task 4. Recruit women undergoing biopsy or surgery to donate a one-time only pre-surgical blood *and* tissue sample, as feasible, at Cedars Sinai Medical Center.

Task 4a: Finalize approach procedures to be used by Dr. Scott Karlan at Cedars-Sinai Medical Center (completed). This task has been completed and the Cedars-Sinai Clinical and Recruitment protocol received DoD Human Subjects approval in July 2005.

Drs. Scott and Beth Karlan have approached physicians who attend Breast Center conferences, to educate them about available research protocols for interested patients. Recruitment flyers and brochures have been posted around the Cedars Sinai campus (specifically, the Saul and Joyce Brandman Breast Center and the Cedars-Sinai Outpatient Surgery Center) and made available to raise patient awareness. This study is also listed on the Cedars-Sinai web site.

Eligible women previously scheduled for a breast surgical procedure that involve the removal of some or all of their breast tissue, are approached about possible study participation. Patients are not scheduled for surgical procedures for the purpose of this study alone. The Principal Investigator, co-investigators, or treating physicians (usually a breast surgeon, occassionaly a radiologist or a medical oncologist) help identify potential subjects. The treating physician makes initial contact with potential subjects and contacts a trained study staff member to consent the patient into the study if the woman agrees to participate.

Task 4b: Routinely approach selected women for blood and tissue collection (starting in month 37). In October 2005, Drs. Beth and Scott Karlan and their study staff began recruiting and enrolling eligible women into the COE study at Cedars Sinai Medical Center. Their study enrollment goal is 50 surgical women per year for the next four years, including women with benign lesions and pre-malignant breast diseases, as well as women with in-situ and invasive carcinoma. Over the last funding period, the Cedars Team has successfully enrolled 87 women with specimen and questionnaire collection from 62% (54 women).

Task 4c: Surgeon to collect benign lesions, atypia, in situ disease, and invasive carcinoma tissue samples. (starting in month 37). As stated above, the Cedars Sinai team has implemented the tissue collection protocol and has collected tissue samples from 83 study participants. Pathology information is centrally abstracted at FHCRC using a Patient Level Clinical Diagnosis form. A summary of patient diagnosis and procedure type where tissue was successfully collected is included below as Table 2. Tissue review and characterization of collected sample(s) stored in the repository will be initiated during the next funding period.

Table 2. Summary Report of Patient Diagnosis by Surgical Procedure at Cedars-Sinai

Population	Sub-Population by Histology	Patients	Collections	Serum (1 mL aliquots)	EDTA-Plasma (1 mL aliquots)	Fresh Frozen Tissue (Vials)
Surgery	Normal (by Reduction Mammoplasty)	1	1	8	6	10
Surgery	NED	1	1	15	7	2
Surgery	Benign	18	18	160	117	67
Surgery	Atypia	10	10	93	71	29
Surgery	In-Situ	13	13	124	94	34
Surgery	Invasive	31	31	207	169	84
Surgery	Pending*	9	9	57	57	7

**pathology report has not been abstracted*

Task 4d: Tissue collected at both FHCRC and Cedars Sinai to be used for molecular profiling work (starting in month 49). Immediately after the surgeon has removed the necessary tissue and the pathologist has taken what is required for pathologic diagnosis, a study Specimen Collection Specialist is permitted to collect specimens from the removed tissue for the purposes of the COE.

All or part of the un-needed tissue is collected, labeled and processed for storage. The tissue is embedded in OCT and/or snap frozen. Tissue collected includes malignant tissue and, if possible, adjacent normal tissue.

We have developed a “Patient Level Clinical Diagnosis” form which uses information that has been abstracted from pathology and other medical reports to characterize a woman based on TNM staging and grade of disease at the time of her diagnosis. An FHCRC study staff member completes this form for all COE surgical participants with the research nurse conducting quality assurance.

Working closely with breast pathologists Drs Sean Thornton and Ellen Pizer of Washington Pathology Consultants, we have created a Breast Histology Tissue Review Form that will be used to characterize all breast tissue samples (see Appendix item C). We are currently in the process of reviewing a pilot group of 120 tissues from 20 patients. To date approximately 50% of the slides in the pilot group have been reviewed. We have also finalized a Clinical Status Follow-Up Form that will capture specific information regarding the patient status after cancer diagnosis and surgery such as treatment, progression or recurrence of the primary cancer and any development of secondary cancers. All of this information will be used to determine which blood and tissue samples are most appropriate for future molecular profiling and marker evaluation work.

Task 5. Blood samples from Mammography and Surgical Cohorts are collected, processed into serum and plasma cryovials, and logged into specimen tracking system (months 26-74).

In all blood collections, the Specimen Collection Specialist collects up to 50 ml of whole blood. At the initial collection the phlebotomist will distribute the blood between 3 red top (serum) tubes, 1 purple top (EDTA plasma) tube, and one yellow top (ACD-plasma and lymphocytes) tube. For all subsequent draws, as included in the FHCRC clinical protocol, the blood is collected in 4 red top tubes and 1 purple top tube.

Standard protocols are followed to process specimens into sera and plasma and aliquoted into cryovials uniquely labeled with study specimen ids. Specimens are then

logged into the specimen tracking system (STS). Typically, the tubes are processed to obtain:

- up to fifteen 1mL aliquots of serum for the initial draw/up to 20mL aliquots for all subsequent draws
- up to five 1mL aliquots of EDTA-Plasma
- two 1.8mL aliquots of ACD-Buffy Coat Cells for the initial draw only
- one ~4mL aliquot of ACD-Plasma for the initial draw only

The blood specimens are stored in 1 ml quantities to avoid damaging freeze-thaw cycles. Aliquoted specimens are entered into the specimen tracking system then transported to the study repository for long-term storage and will eventually be delivered to laboratory investigators for future analysis. Blood draw date and time, and time of processing and freezing are recorded in the specimen tracking system, as well. A summary of serum, plasma, and tissue samples stored in the COE repository at Fred Hutchinson is included below as Table 3.

Table 3. COE Repository Report for specimens collected by Fred Hutchinson Team

Population	Sub-Population by Histology	Patients	Collections	Serum (1 mL aliquots)	EDTA-Plasma (1 mL aliquots)	ACD-Plasma (4 mL aliquots)	ACD Buffy Coat (1.8 mL aliquots)	Fresh Frozen Tissue (Vials)	OCT-Embedded Tissue (Blocks)
Mammography	Normal	461	648	9430	3224	564	1068	0	0
Surgery	Benign	8	12	144	52	11	22	3	9
Surgery	Atypia	2	3	29	12	3	6	0	0
Surgery	In-situ	26	54	708	251	47	90	5	6
Surgery	Invasive	145	279	3543	1232	230	448	342	322
Surgery	NED	1	3	36	13	2	4	0	0
Surgery	Pending*	32	49	654	230	44	58	37	62

**Pathology report has not been abstracted*

Task 6. Revise existing ovarian cancer database to accommodate breast tissue specimens and questionnaire

Task 6a: Analyze **current system** and prepare preliminary assessment of revised software design specifications (completed). As previously reported, FHCRC programmers have enhanced an existing specimen tracking system (STS) to accommodate specimens and breast specimen data being collected as part of the COE. Currently tracked for COE specimens are date of blood and/or tissue donation, specimen processing, amount of specimen collected, types of specimen storage, and storage location of specimen aliquot or tissue vial or block. A screenshot of the breast specimen tracking is included below.

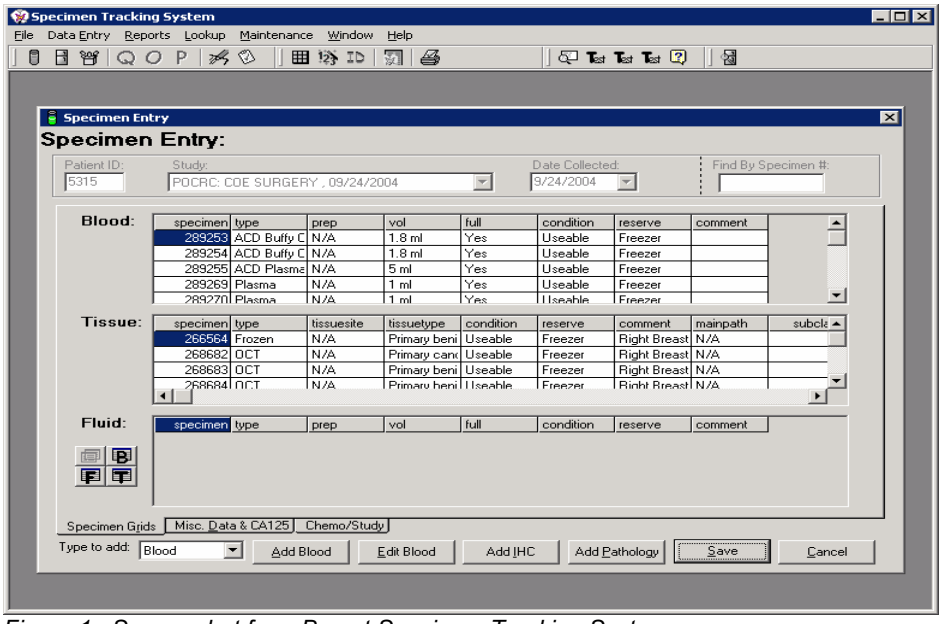


Figure 1: Screen shot from Breast Specimen Tracking System

Task 7. Develop an implementation test utilizing proposed software with a middle tier and internet interface for the Clinical Data Module (completed).

As previously reported, we have prepared much of the informatics infrastructure required to support the COE study. Infrastructure in place include: web server hardware, web service software, access security, data entry form templates, and referential integrity between database objects. We have refined an Access database to track information that is collected on our Patient Level Clinical Diagnosis Form. As stated above, this form provides appropriate information to characterize a woman based on TNM staging and grade of disease at the time of her diagnosis. It also captures receptor status information, such as estrogen or progesterone positivity/negativity, which will be used to select specimens for the different specimen sets. The Access database acts as our "clinical module" and is linked to SIM, our primary data management system, which in turn is linked to the Specimen Tracking System. (STS).

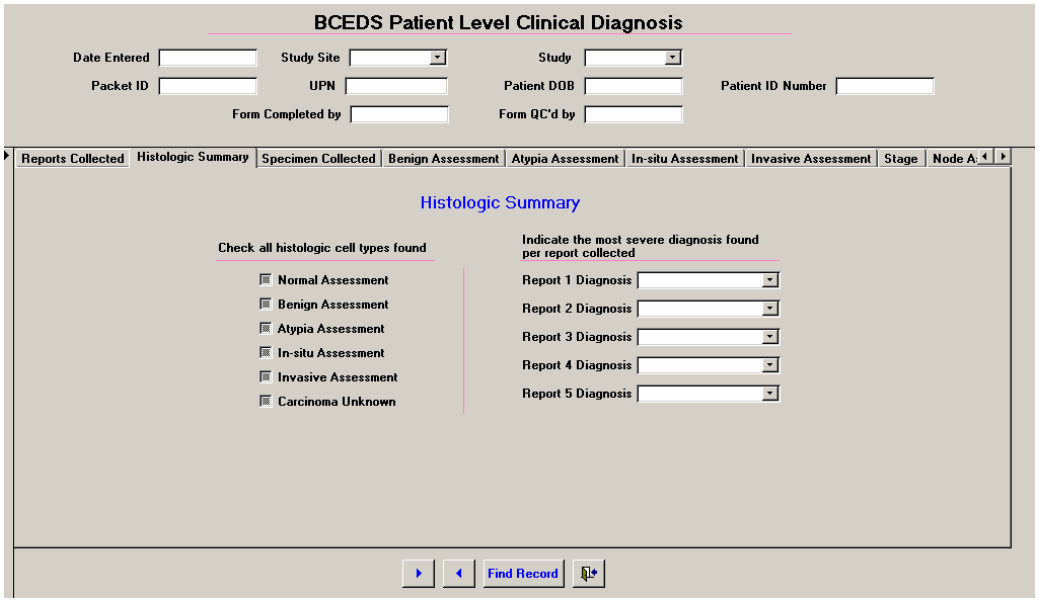


Figure 2: Screen shot of Patient Level Clinical Diagnosis data entry in Access database

Web based screens for questionnaire data entry have been developed and are currently in use by the two COE recruitment sites: FHCRC and Cedars Sinai. Routines for data

validation with each submission of data to the server have been implemented. Every value entered is checked for validity. Any outliers are returned to the data entry specialist for verification before the data are committed to the database. In addition, attempts to re-enter data that have previously been collected, are preempted via referential integrity. The screen shot below minimally illustrates the kinds of validation that data entry specialists see prior to the acceptance of data by the database.

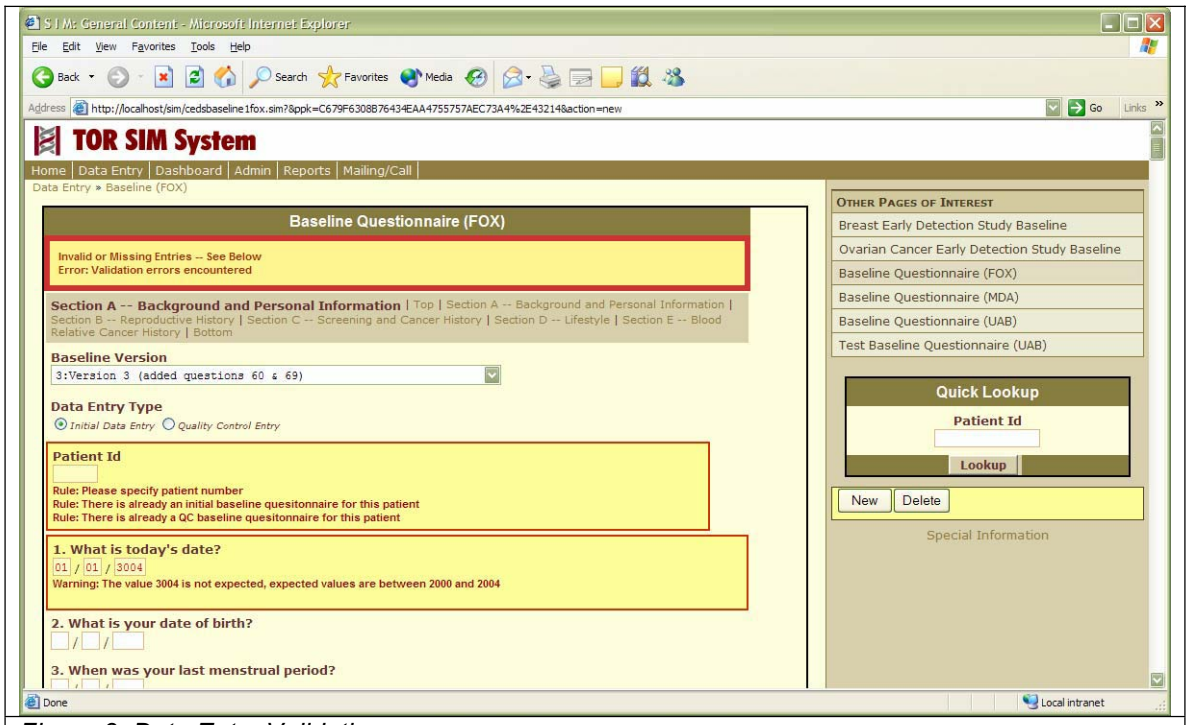


Figure 3: Data Entry Validation

Task 8. Develop breast specimen tracking database to replicate and enhance the current system's functionality adjusting per information gained in the implementation test (months 40-52).

Dr. Michèl Schummer, Staff Scientist, developed SpecimenDB, a FileMaker database for information that is generated from our specimens, such as experimental and specimen processing results. SpecimenDB also serves as a front-end to COE databases SIM, STS and the Access database tracking our Patient Level Clinical Diagnosis Form. The interface provides a unified look across all components and is thus easy to navigate. Each field can be searched without knowledge of the underlying structure. Summary reports can be generated from any view as Excel or PDF documents. SpecimenDB is client- and web-based, the latter allowing for collaboration across sites. Although the back-end consists of several databases, the user sees just three major areas: Specimens, Patients and Results.

The Specimens area holds data about the processing of the specimens, such as RNA extraction (Figure 4a). This allows for technicians to enter information pertaining to specimen processing. Having this information in a central location will prevent us from distributing a specimen that was previously known to yield poor RNA or protein. The Specimens area also has a view that lists multiple specimens in rows which allows for intuitive searches and the generation of summary reports (Figure 4b).

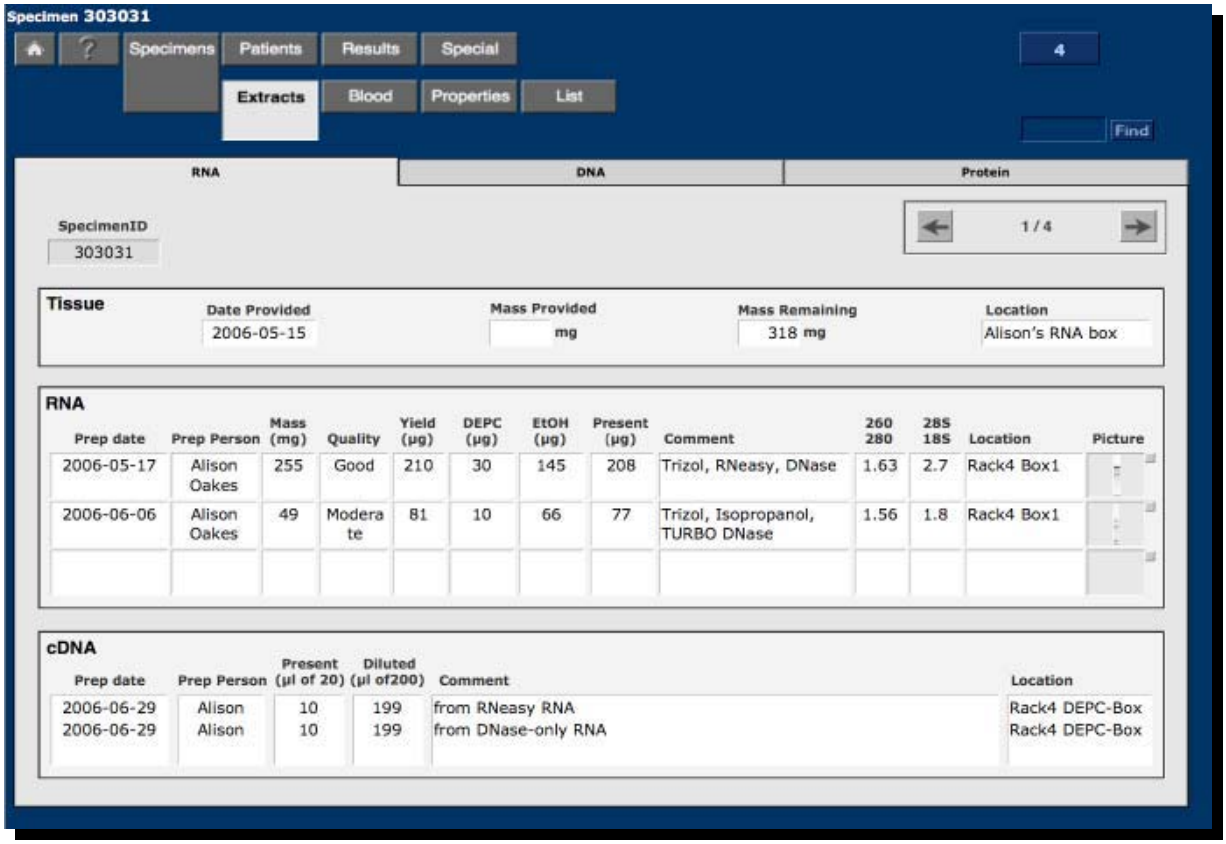


Figure 4a: Specimen extracts view

Figure 4b: Specimen list view based on patients selected in the patient list view

The Patients area holds patient-related information that has been stripped of any identifying information, including the pathology reports, both abstracted and a scanned copy. Similar to the specimen area, it is possible to toggle between views that list detailed information about a single or multiple patients. In list view, it is further possible to toggle between patients and their specimens.

The Report area is designed to contain experimental data obtained from the specimens in our repository. Implementation of interface and functionality will be decided upon when data are available for upload (spring of 2007).

Task 9. Develop collaborative web site

Task 9a: Develop site to support real-time discussion and information sharing among investigators (Completed). Investigators and study staff utilize the Computational Portal Analysis System (CPAS) website, created by Dr. Martin McIntosh and his Computational Proteomics Laboratory group at the Fred Hutchinson Center. CPAS is an open-source science portal offering web-based bioinformatics and collaboration tools to help scientists store, analyze and share data from high-throughput experiments and clinical trials. CPAS is available as free, installable software, with source code. This work is being done as part of a project funded by an NCI subcontract (23XS144A).

One of the features available on CPAS is a wiki based project management tool. COE investigators and staff and have been trained to use this project management and communication tool. Staff continue to use the study website to support real-time communication and information sharing among FHCRC staff, COE investigators and their respective staff. A username and password are required to access information on this site. The content on CPAS is organized hierarchically into projects and subfolders, much like the file directories on your computer; therefore, users find it easy to navigate through and use. The left side of each CPAS web page displays this tree-like structure as shown below.

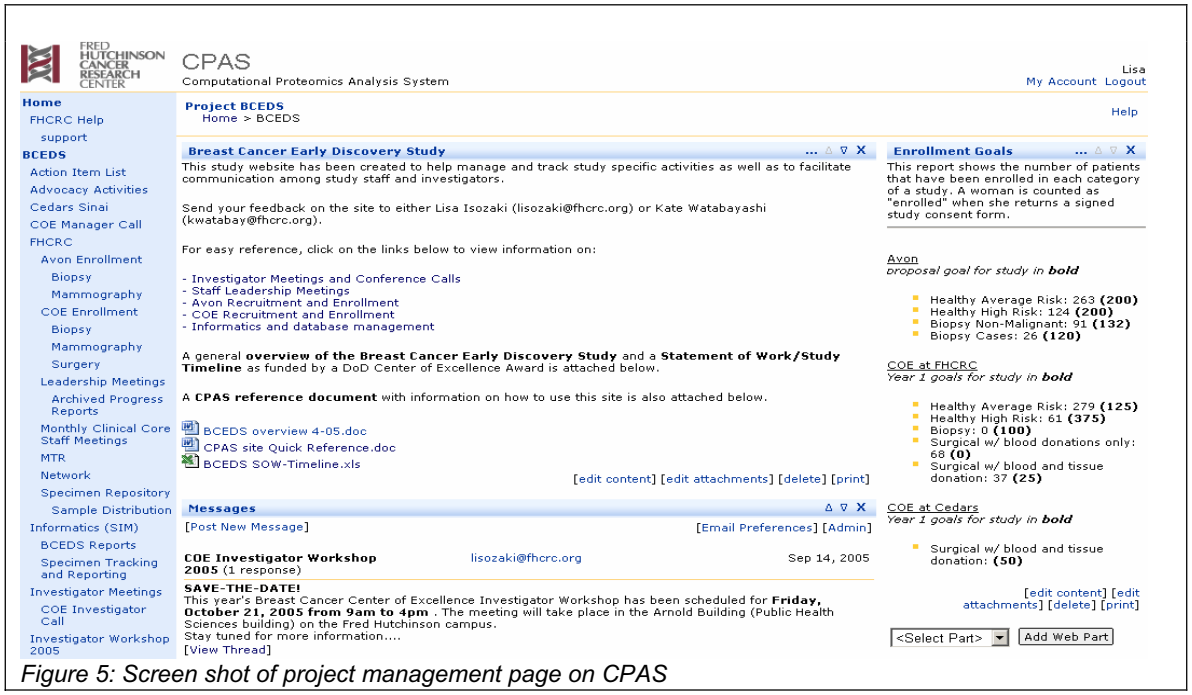
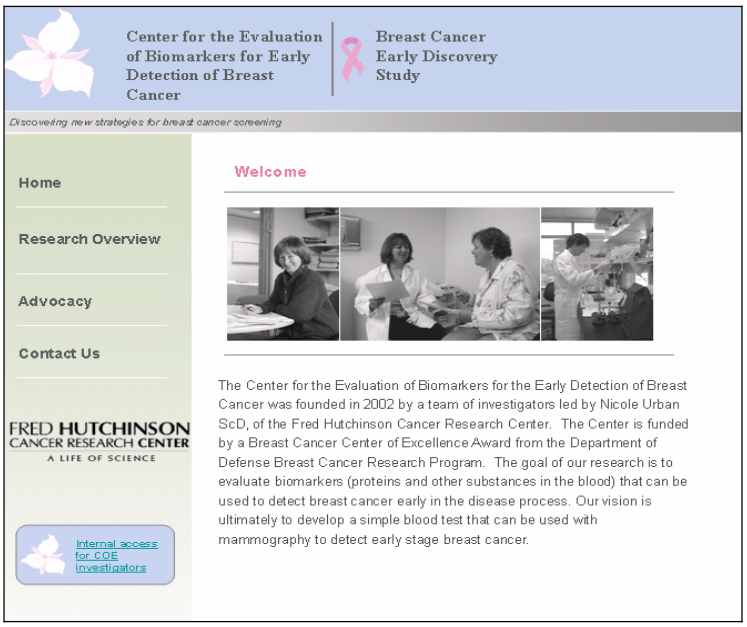


Figure 5: Screen shot of project management page on CPAS

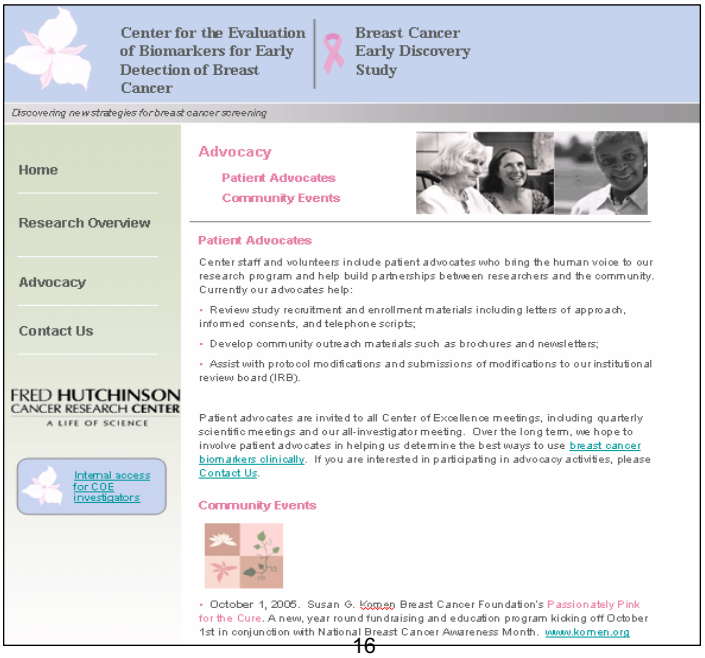
There are several useful features, which support real-time interactive communication among users. First, one is able to post messages on a message board. Once the message is posted, an automatic alert is sent out to other users letting them know a

message has posted. Second, one is able to post documents with ease, using simple attachment buttons or by creating a link to documents stored on a shared drive. These documents can be easily accessed or downloaded by others through the online portal. The system also serves as an archive with all messages and documents stored in system data files.

In addition to CPAS, we are currently in the process of creating a second website to function as a study reference to outside researchers and the general public. A mock-up of the home page is copied below.



The website will consist of three main sections: a Homepage, Research Overview, and Advocacy. The Research Overview will contain pages dedicated to the following areas of the study: overview of the research team, study population, specimen collection procedures, biomarker evaluation and marker panel development, and the clinical relevancy of a panel. The Advocacy page will provide an overview of our breast advocacy program and a list of upcoming community events focused on patient advocacy, breast cancer awareness, health education and wellness.



Lastly, COE investigators and staff may access CPAS directly from the site by clicking on the “Internal Access for COE Investigators” button also located in the link sidebar. The website will be maintained and updated on a regular basis by study staff.

Task 9b: Develop extensions that will give investigators ability to query specimen tracking system and download summary reports (Month 32-42). In spite of its name, SpecimenDB (explained in detail under Task 8) tracks both specimen and patient related (clinical) information. Its unification of several databases allows investigator-generated queries. For example, a user can select patients that match certain clinical criteria and click on the “toggle specimens” button. Available specimens matching the criteria will be shown. The user can then search for subsets of these specimens, such as available serum volume. Queries can be performed in increments, which will allow the investigator to review the data between steps. Multiple AND or OR statements can be applied without knowledge of the underlying database structure.

Once a subset of records has been identified, a summary report can be generated through pre-configured templates, or ad-hoc, through user-selection. To facilitate this process, field names are the same in the user interface as in the underlying database.

In addition, the COE CPAS site is linked to the study’s data management system; therefore, investigators are able to access and view data reports as if they were in the SIM system as illustrated by the screen below.

Task 9c: Develop web pages for each investigator that are linked to collaborative site (Completed). We have developed folders on CPAS for each laboratory based investigator. Each investigator will be able to design their own folder and create subfolders suiting their specific needs; however, we will request that investigators use their folders to upload all laboratory results and to view marker results.

We have also developed folders to support investigator specific meetings and collaborative activities, such as the quarterly investigator calls and the developing Specimen Review Committee. In addition, we have created a folder that is open to the public to support the upcoming COE investigator meetings such as our annual workshop on November 3, 2006. All workshop materials are currently posted on this site and are easily accessible by clicking on the following link: https://proteomics.fhcrc.org/CPAS/Project/BCEDS/Investigator%20Meetings/Annual%20COE%20Workshop/begin.view?

Task 10: Prepare and Analyze Breast Mini-Triage Set (Formerly called ARTS)

Task 10a: Provide blinded samples from a set of 80 women to laboratory investigators (months 49-54). Investigators are now beginning to prepare the first specimen set, the Breast Mini-Triage Set (BMTS) that will be provided to study laboratory investigators to determine the preliminary usefulness of new markers. This set will be composed of 40 cases and 40 controls, with a total of 80 serum samples. Currently our statisticians are reviewing specimen availability to determine which ones should be included in the BMTS taking into account variables such as stage, histology and receptor status (for cases), menopausal status, age, and breast density. The BMTS will also be available to new collaborators that may have promising markers ready for evaluation. For example, we plan to collaborate with COE recipient Dr. Saraswati Sukumar of Johns Hopkins on markers of interest including HOXB-7, HEYL and SPARC, and Dr. Kornelia Polyack of the Dana Farber Cancer Institute on Psoriasin (S100A7). Dr. Thea Tlsty from UCSF has also expressed interest in working with us on markers to detect circulating tumor cells.

Tasks 10b and 10c: Statistical analysis of BMTS results and continued assay refinement (months 51-55). We anticipate conducting statistical analyses on preliminary assay results from the BMTS around month 51, and will provide results to laboratory scientists in months 52-55 for continued assay refinement.

Tasks 11-13: Biomarker Panel Validation and Evaluation (months 55-72)
Once statistical analyses of the BMTS results are complete, investigators will begin putting together the Panel Development and Validation Sets. To help us identify a marker panel with a high level of sensitivity and specificity, we will continue to seek additional collaborators who may have promising markers available for evaluation.

Key Research Accomplishments

- Study Accrual – on target to meet most of our accrual goals through two complete years of study enrollment.

	Cumulative Accrual Goals	TOTAL Actual Accrual
Mammography Cohort -- High/Elevated Risk	450	438
Mammography Cohort – Average Risk	150	36
Risk Status pending		125
Mammography Cohort – Biopsy	200	0
Subtotal: Mammography Cohort	***800***	***599***
SMC Surgical Cohort: Blood and Tissue	75	88
SMC Surgical Cohort: Blood Only+	100	172
SMC Surgical Cohort: no specimen donation		9
Subtotal: Surgical Cohort	***175***	***269***
Cedars Biopsy Cohort: Blood and Tissue	100	87
Total	**1075**	**955**

- COE Repository of donated blood and tissue specimens - a well-characterized specimen repository of serum, plasma, and fresh frozen tissue has been established, with new and serial collections on-going. Stored specimens in the repository will be used by COE investigators to evaluate markers and conduct molecular profiling work over the next year.

Population	Sub-Population by Histology	Patients	Collections	Serum (1 mL aliquots)	EDTA-Plasma (1 mL aliquots)	ACD-Plasma (4 mL aliquots)	ACD Buffy Coat (1.8 mL aliquots)	Fresh Frozen Tissue (Vials)	OCT-Embedded Tissue (Blocks)
Mammography	Normal	461	648	9430	3224	564	1068	0	0
Surgery	Benign	8	12	144	52	11	22	3	9
Surgery	Atypia	2	3	29	12	3	6	0	0
Surgery	In-situ	26	54	708	251	47	90	5	6
Surgery	Invasive	145	279	3543	1232	230	448	342	322
Surgery	NED	1	3	36	13	2	4	0	0
Surgery	Pending*	32	49	654	230	44	58	37	62

- Study website (www.breastbiomarkers.net)will strengthen communication among COE investigators and will enhance study visibility. We anticipate that the site will go live in early 2007.

Reportable Outcomes

Resources have been devoted to support the work of Dr. Nathalie Scholler, FHCRC Senior Staff Scientist, and laboratory technicians in the Translational and Outcomes Research (TOR) lab (PI: Nicole Urban) to develop bead based ELISA style assays for candidate early detection biomarkers. The bead based assays are run on BioPlex Suspension Array Systems located in the TOR lab (Luminex based technology). To date, the TOR lab team has been able to develop, optimize, and validate bead based assays for several known ovarian markers including CA-125, HE4, and Mesothelin. To meet the aims of this COE, Dr. Scholler will develop bead based assays for candidate breast markers including CD 24, Prolactin, and Mammaglobin using yeast-secreted, in vivo biotinylated scFv recombinant antibodies, or *biobodies.*

In a paper recently accepted for publication in the *Journal of Immunological Methods*, Dr. Scholler and colleagues show that biobodies permit cost-effective generation of biotinylated recombinant antibodies of high affinity that, in turn, permit validation of candidate biomarkers at a more rapid and efficient rate. Biobodies are secreted by diploid yeast resulting from the fusion of two haploid yeast of opposite mating type. One yeast carries a cDNA encoding an antibody recognition sequence fused to an IgA1 hinge and a biotin acceptor site (BCCP) at the C-terminus; the other carries a cDNA encoding an E.Coli biotin ligase (BirA) fused to KEX2 golgi-localization sequences, so that BirA can catalyze the biotin transfer to the recognition sequence-fused BCCP within the yeast secretory compartment. In this manuscript, investigators illustrate this technology with biobodies against HE4, a biomarker for ovarian carcinoma. Anti-HE4 biobodies were derived from clones or pools of anti-HE4-specific yeast-display scFv, constituting respectively monoclonal (mBb) or polyclonal (pBb) biobodies. Anti-HE4 biobodies were secreted directly biotinylated thus bound to labeled-streptavidin and streptavidin-coated surfaces without Ni-purification. Anti-HE4 biobodies demonstrated specificity and sensitivity by ELISA assays, flow cytometry analysis and western blots prior to any maturation; dissociation equilibrium constants as measured by surface plasmon resonance sensor were of Kd= 4.8x10-9 M and Kd=5.1x10-9 M before and after Ni-purification respectively.

As encouraged at the recent COE workshop in Arlington, Virginia, resources may also be devoted to conduct some discovery work in both serum and breast tissue, since there are not enough candidate markers currently ready or available for evaluation. COE investigators, Drs. Beth Karlan and Michel Schummer, have begun discussing the use of current technologies to study and compare the expression of genes in tissues from

normal healthy women versus women with known malignant breast cancer. Previous work in ovarian cancer has shown that genes that are highly expressed in malignant tissue, but expressed at low levels in healthy tissue are quality candidates for development as diagnostic markers.

As mentioned above, investigators and study staff use the Computational Portal Analysis System (CPAS) website, created by Dr. Martin McIntosh and his Computational Proteomics Laboratory group at the Fred Hutchinson Center to support real time communication and project management issues associated with this study. CPAS is an open-source science portal offering web-based bioinformatics and collaboration tools to help scientists store, analyze and share data from high-throughput experiments and clinical trials. CPAS is available as free, installable software, with source code, and can be downloaded at: http://cpas.fhcrc.org.

Conclusions

No research conclusions are available at this time.

Appendices

Appendix A *Women's Cancer Prevention and Detection* newsletters
Appendix B 2005 All-Investigator Workshop Meeting Agenda
Appendix C Breast Histology Tissue Review Form

WOMEN'S CANCER PREVENTION *and* DETECTION NETWORK

NEWS BULLETIN

Autumn 2006

Awareness Is the Key to the Prevention and Early Detection of Women's Cancers!

Welcome to the fall edition of the Women's Cancer Prevention and Detection Network Newsletter! September and October are very important months for our Network participants as September is ovarian cancer awareness month and October is breast cancer awareness month. Because ovarian cancer is often diagnosed late in the disease process and breast cancer strikes over 200,000 women per year, it is extremely important that we are educated about these cancers.

Ovarian cancer occurs in 1 out of 55 women and is usually diagnosed when the chance for survival for 5 years is about 25%. A pap smear is not an effective detection method for ovarian cancer. Historically, ovarian cancer has been labeled the Silent Killer because of its lack of symptoms. Research studies performed here in Seattle, however, contradict this notion. According to the results of the Symptoms Study, published in 2004 JAMA, the majority of women diagnosed with ovarian cancer consistently report symptoms to their physicians - even with early stage ovarian cancer. Women should check with a physician or other health-care professional if they have one or more of these new symptoms which persist for more than three weeks:

- Abdominal swelling or bloating
- Abdominal or pelvic pain or pressure
- Gas, indigestion, nausea or changes in bowel habits
- Vaginal bleeding or discharge
- Urinary urgency, burning or spasms

Studies at the Center are ongoing with the hope that eventually all physicians will use a symptoms checklist for ovarian cancer at a woman's annual checkup that will enable doctors to detect ovarian cancer early, when it is most treatable.

In the United States, breast cancer is the most common non-skin cancer and the second leading cause of cancer-related death in women (source: cancer.gov). Early breast cancer does not usually cause pain, but some common symptoms include:

- A change in how the breast or nipple feels

continued on next page

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A LIFE OF SCIENCE

continued from front cover

- A lump or thickening in or near the breast or in the underarm area
- Nipple tenderness
- A change in how the breast or nipple looks
- A change in the size or shape of the breast
- A nipple turned inward into the breast
- The skin of the breast, areola, or nipple may be scaly, red, or swollen. It may have ridges or pitting so that it looks like the skin of an orange.
- Nipple discharge (fluid)

Most often, these symptoms are not due to cancer, but any woman with these symptoms should tell her doctor so that problems can be diagnosed and treated as early as possible. The American Cancer Society believes the use of mammography, clinical breast examination, and breast self-examination, according to the recommendations outlined above, offers women the best opportunity for reducing the breast cancer death rate through early detection.

Below is a cancer related health observances calendar. Please take the opportunity to learn more about each cancer during these months for awareness is the key to the prevention and early detection of all cancers. If you have any further questions about cancer in general, contact the National Cancer Institute at phone number/website.

Upcoming Cancer Awareness Months

January	Cervical Health Awareness Month
March	National Colorectal Cancer Awareness Month
May	Melanoma/Skin Cancer Detection and Prevention Month
September	Ovarian Cancer Awareness Month Childhood Cancer Month Leukemia and Lymphoma Awareness Month Prostate Cancer Awareness Month
October	Breast Cancer Awareness Month Oct 20 – National Mammography Day
November	Lung Cancer Awareness Month Pancreatic Cancer Awareness Month

Annual Report to the Nation Finds Cancer Death Rates Continue to Drop

A new report from the nation's leading cancer organizations finds that Americans' risk of dying from cancer continues to drop. The authors attribute the decrease in death rates, in part, to successful efforts to reduce exposure to tobacco, earlier detection through screening, and more effective treatment, saying that continued success will depend on maintaining and enhancing these efforts.

Despite this good news, the overall rate of newly diagnosed cancers for both sexes and all races combined has not dropped, but has been stable from 1992 to 2003. The good news about the incidence rates for female breast cancer is that from 2001 to 2003; rates have stabilized, ending increases that began in the 1980s. The factors that influence breast cancer incidence are complex, including changes in reproductive risks, obesity, age-cohort effects, and the prevalence of mammography screening, among others. Recent reports hypothesize that the stabilization of breast cancer incidence may be related to the rapid discontinuation of hormone replacement therapy, a known risk factor for breast cancer. Change, even stabilization, in mammography screening prevalence also affects incidence trends. Whether this first indication of a changing trend is a real or random fluctuation cannot be determined until data reporting in the next few years is complete.

The incidence rate for ovarian cancer also dropped from 1992 to 2003, but mortality rates remain stable. To view the full report, go to ***www.interscience.wiley.com/cancer/report2006.***

Chef Rocky H. Aoki Benihana Fried Rice

Flocked with colorful vegetables, this recipe is quick and easy to make. It's a great way to use up your leftover take-out rice!

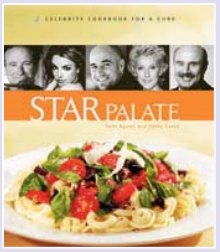
Benihana Fried Rice

4 teaspoons peanut or other vegetable oil
2 eggs, beaten
2 tablespoons chopped onion
2 tablespoons chopped green onion
2 tablespoons chopped carrots
4 cups steamed white rice
1 cup chopped cooked chicken
1 teaspoon sesame seeds
¾ teaspoon salt, optional
¼ teaspoon black pepper
2 tablespoons butter
4 teaspoons soy sauce

Heat a 12-inch nonstick skillet or wok over medium heat. Add 1 teaspoon oil and scramble the eggs until just firm. Remove from the pan and let cool; then chop the eggs and reserve.

Meanwhile, add the remaining 1 tablespoon oil to the pan, and raise the heat to medium-high. Sauté the onion, green onion, and carrots until tender, about 2 to 3 minutes. Mix in the rice, chicken, and chopped eggs. Add the sesame seeds, salt, and peeper, stirring well. Add the butter and soy sauce to the mixture, stirring until well combined.

Makes about 8 servings.



Recipe taken from Star Palate, co-authored by Tami Agassi and Cathy Casey, published by Documentary Media. Star Palate is available at major booksellers and at ***Amazon.com***. All proceeds will benefit the Marsha Rivkin Center for Ovarian Cancer Research and The Breast Cancer Research Foundation.

Cookbooks can be purchased in person at the Marsha Rivkin Center, 1221 Madison, Suite 1401, (206) 215-6200 for $10 each.

Highlights from the 2006 Breast Cancer Research Program—Centers of Excellence Meeting

by Kate Watabayashi

On July 26 and 27th the Department of Defense Breast Cancer Research Program (BCRP) held the 2006 Centers of Excellence (COE) Meeting, bringing together researchers, patient advocates and study staff from ten states representing fourteen institutions who have received BCRP funding to establish a Center of Excellence in breast cancer. The Program's mission is to foster new directions, address neglected issues and bring new investigators into the field of breast cancer research with the goal of eradicating the disease. The Centers focus on a wide range of breast cancer issues including prevention, treatment and improving patient care settings. Below are research highlights for Centers that have recently published new findings:

- **Alcohol Consumption and Breast Cancer Risk:** This Center is studying how alcohol affects breast cancer risk by looking at the effects of diet, drinking and genetic changes on different biological pathways that are related to the development of breast cancer. Researchers think that alcohol may increase breast cancer risk by several mechanisms, including damage to DNA and proteins, and interfering with folic acid intake resulting in genetic changes that could lead to inactivation of tumor suppressor genes (genes that prevent cancer from developing). (Georgetown University, ***http://lombardi.georgetown.edu/research/COE/index.html,*** August 16, 2006)
- **Racial Disparities in Breast Cancer:** This Center aims to identify barriers that prevent women with non-metastatic breast cancer from receiving optimal treatment, to identify any racial differences among these barriers, and to see if these differences play a part in cancer survival. Researchers have recently reported that race was one of several factors associated with a delay in starting adjuvant radiotherapy (treatment using radiation to kill cancer cells) after surgery. (Hershman DL et al. Int J Radiot Oncol Biol Phys. 2006)

For more information about these and other Centers of Excellence, please visit: ***http://cdmrp.army.mil/bcrp/coeawards.htm***.

The Marsha Rivkin Center for Ovarian Cancer Research Continues to Raise Funds and Awareness!

On July 23rd, more than 3,200 participants supported ovarian cancer research by participating in the 12th annual Swedish SummeRun. This was a record breaking year for this annual event, raising more than $400,000 for the Marsha Rivkin Center for Ovarian Cancer Research. A sea of ovarian cancer survivors wore teal t-shirts and were asked to come to the stage for a special tribute in their honor. Two special survivors and network participants, Joyce McCallum & Susan Dearborn, served as honorary chairs of the race and as shinning examples of courage and strength. Thanks to Swedish Medical Center, 100% of dollars raised benefited the Rivkin Center.

On September 7th and 8th, more than 280 researchers, medical clinicians and patients convened in Seattle for the 6th Biennial Ovarian Cancer Research Symposium: From Prevention to Cure. This nationally recognized conference examined the latest and most innovative research in ovarian cancer and addressed many controversial issues in both research and the treatment of this disease. The conference featured over 50 presentations in two days from 7 countries. Speakers represented many of the major cancer centers of the United States, as well as those of Canada, England, Israel, Germany, Greece and Australia. This year's conference also included breakout sessions developed for nursing professionals and patient advocates. For further information about Rivkin Center visit ***www.marsharivkin.org.***

Contact Us

Are you moving? Do you have any questions about our research studies or suggestions for articles or features to improve our newsletter? Please call Shannon at ***206-667-4587*** or email at ***smarsh@fhcrc.org*** to keep us updated or to request information at any time. We welcome your feedback!

Women's Cancer Prevention and Detection Network
P.O. Box 19024
Mail Stop M2-B230
Seattle, WA 98109

Center of Excellence All-Investigator Workshop

October 21, 2005

Center for the Evaluation of Biomarkers for Early Detection of Breast Cancer
Fred Hutchinson Cancer Research Center
Day Campus, Arnold Building 4th floor (M4-A805/817)

8:30am	**Continental Breakfast**
9:00 am	**Opening remarks: Status of Marker Evaluation** *-Nicole Urban, ScD (Hutchinson Center)*
	Morning Session
9:45am	**Tissue Collection Concerns and Priorities** *- Scott Karlan, MD (Cedars-Sinai Medical Center)*
10:15am	**Tumor Cells in Blood of Breast Cancer Patients** *- J. David Beatty, MD (Swedish Medical Center*)
10:45am	**Morning Break**
11:00am	**Circulating Antibodies as Early Detection Markers** **-** *Nora Disis, MD (University of Washington)*
11:30am	**Salivary Diagnostics for Breast Cancer** *- David Wong, DMD, DMSc (UCLA)*
12:00pm	**Lunch**
	Afternoon Session
1:00pm	**Assay Development in the TOR Lab** *- Nathalie Scholler, MD, PhD (Hutchinson Center)*
1:30pm	**An Overview of Computational Proteomics Laboratory Informatics Developments** *- Martin McIntosh, PhD (Hutchinson Center)*
2:00pm	**Break**
2:15pm	**Opportunities to use Biomarkers Clinically** *- Scott Ramsey, MD, PhD (Hutchinson Center*)
2:45pm	**A Patient's Perspective** *- Shannon Marsh (Hutchinson Center*)
3:15pm	**Discussion- Current progress and future directions**
4:00 pm	**Closing**

Breast Cancer Early Discovery Study – *Tissue Specimen Review*

Date of analysis: ____/____/_____ Pathologist :_____

Patient ID/UPN:	Specimen ID:			Specimen ID:			Specimen ID:		
	Dx	%	*Grade	Dx	%	*Grade	Dx	%	*Grade
Diagnosis 1									
Diagnosis 2									
Diagnosis 3									
% Normal									
% Viable tumor cells									
% Necrosis of total tumor cells									
% Inflammatory component of total specimen cellularity									
Lymphatic/Vascular Invasion Present:	Yes No *(Circle One)*			Yes No *(Circle One)*			Yes No *(Circle One)*		
Calcification Present:	Yes No *(Circle One)*			Yes No *(Circle One)*			Yes No *(Circle One)*		
Calcification Associated with: *(Circle or check all that apply)*	Benign Atypia DCIS Invasive			Benign Atypia DCIS Invasive			Benign Atypia DCIS Invasive		

***Nuclear Grade** – for in-situ diagnosis, use the following:

1 Well differentiated
2 Moderately differentiated
3 Poorly differentiated

***Histologic Grade (Modified Bloom-Richardson System)** – for invasive diagnosis, use the following:

I Low grade (MBR Score 3-5)
II Intermediate/Moderate (MBR Score 6-7)
III High (MBR Score 8-9)

Pathology Diagnosis (Dx) – For each specimen, please use the numbering system below representing one diagnosis and write it in the cells under "Dx".

1 Proliferation without atypia
5 Fibroadenoma
11 Radial scar
14 Phylloides, Low grade
15 Phylloides, High grade

21 Proliferation with atypia

31 Lobular Carcinoma In-situ (LCIS)

32 DCIS: Clinging
33 DCIS: Papillary
34 DCIS: Intracystic
35 DCIS: Apocrine
36 DCIS: Micropapillary
37 DCIS: Cribriform
38 DCIS: Solid
39 DCIS: Comedo

41 Invasive: Ductal, NOS
50 Invasive: Lobular
48 Invasive: Mixed ductal / lobular, NOS
49 Invasive: Mixed (*Other*) *Specify*_____
42 Invasive: Medullary
43 Invasive: Atypical Medullary
44 Invasive: Mucinous
45 Invasive: Papillary
46 Invasive: Micropapillary
47 Invasive: Tubular
51 Invasive: Adenoid cystic
52 Invasive: Metaplastic
53 Invasive: Squamous
55 Invasive: Sarcoma *Specified*_____

90 Other_____
91 Other_____
92 Other_____

Comments:

For Office Use Only

Data Entry By:
Data Entry QC By: